Accuracy and clinical utility of the tumor grade- and stage-centered predictive model in localized upper tract urothelial carcinoma

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Abstract

Background: Among various clinicopathological factors to identify low-risk upper tract urothelial carcinoma (UTUC), tumor grade and stage are of utmost importance. However, clinical value added by combining other risk factors remains unproven.

Objective: To assess the performance of a tumor grade- and stage-centered (GS) selection model in identifying UTUC patients who can attempt kidney-sparing surgery.

Design, setting, and participants: In this international study, we reviewed the medical records of 1,240 patients with UTUC who underwent radical nephroureterectomy. Complete data needed for risk stratification according to the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines were available in 560 patients.

Results: Overall, 198 (35%) patients had clinically low-grade, non-invasive tumors, and 283 (51%) had ≤pT1disease. Multivariable analyses revealed that none of the EAU and NCCN risk factors was associated with the presence of non-muscle invasive UTUC in patients with low-grade and low-stage UTUC. Of all the models, the GS model exhibited the highest accuracy, sensitivity, and negative predictive value. According to the GS, EAU and NCCN model, the proportion of eligible patients was 35%, 6% and 4%, respectively.

On DCA, the net benefit of the three models was similar within the clinically reasonable range of thresholds.

Conclusions: The grade- and stage-centered model showed a favourable predictive accuracy and identified the greater number of eligible patients than the EAU and NCCN models. The decision-making algorithm that weighs the benefits of avoiding unnecessary kidney loss against the risk of undertreatment in case of advanced carcinoma is necessary for individualized treatment in UTUC patients.

Patients summary: For patients with clinically low-grade, low-stage upper tract urothelial carcinoma (UTUC), none of other risk factors was associated with the better prediction of localized UTUC. The grade- and stage-centered model may help establish the weighted algorithm to identify patients who benefit from conservative treatment.

Keywords: upper tract urothelial carcinoma, conservative treatment, KSS, predictive model, low-grade

Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision (with or without lymphadenectomy) remains the standard of care for patients with high-risk nonmetastatic uper tract urothelial carcinoma (UTUC) (1-4). Kidney-sparing surgery (KSS), including segmental ureterectomy and endoscopic ablation, has been discussed as an alternative treatment option for three decades now. However, the development of an accurate preoperative staging method for UTUC is crucial to expanding the indication for KSS so that all patients who are potentially to benefit from KSS have the chance to do so (5). To overcome the limitation of inaccurate preoperative staging, the current guidelines recommend a risk stratification strategy for decision-making and patient counseling, which has combined previous identified risk factors (3, 6). Several preoperative models have successfully validated the utility of strategies that consider a combination of these risk factors (7, 8). Nevertheless, according to the National Cancer Database, <20% of patients with low-grade UTUC receive endoscopic treatment (9), indicating that the current criteria for KSS might be too stringent. Brien et al. were the first to provide a predictive model with remarkable accuracy; they found that three variables (presence of hydronephrosis, tumor grade on biopsy, and urinary cytology findings) provided a negative predictive value of 100% for muscle-invasive or non-organ-confined UTUC (10).

However, in their study, only 8% of patients met these criteria at the cost of pursuing the predictive accuracy, and many remaining patients are likely to have received overtreatment. Therefore, optimizations of the current risk stratification strategy without comprising oncologic safety are needed to find the sweet spot between over- and under-treatment.

The most established independent risk factors are ureteroscopy (URS)-based tumor grade and clinical imaging-based tumor stage (11). Tumors presumed to be low-grade, and low-stage UTUC have been managed successfully using KSS (12). For clinically low-grade, low-stage tumors, other risk factors limit the adaption of KSS, but the value that they add in risk prediction remains still unproven in well-designed validation studies. Thus, we sought to evaluate the clinical value of each risk factor in patients presumed to have low-grade, low-stage UTUC in order to refine the selection of patients well-suited to undergo KSS.

Materials and Methods

Eligible patients

This multicenter retrospective analysis was approved by the institutional review boards of all participating institutions. We retrospectively reviewed the medical charts of 1,240 patients with clinically non-metastatic UTUC who underwent URS biopsies followed by

RNU between 2000 and 2016 at 16 academic centers from Europe, North America, and Eastern Asia. Computerized datasets were generated for merging. Through regular communication with all institutions, all identified discrepancies were resolved prior to analysis, and the final dataset was produced for the current analysis. RNU was performed using an open or laparoscopic approach, with distal ureter management at the surgeon's discretion. Bladder cuff excisions were performed via extra- or trans-vesical approach (4). Lymphadenectomy was also performed at the surgeon's discretion; extended lymphadenectomy was not routinely performed (13). Patients who received neoadjuvant chemotherapy for UC, those who underwent conservative treatment, and those for whom we could not determine tumor grade using URS were excluded from the analyses. Based on the guidelines' risk classifications, only patients with complete data were included in this analysis.

Predictive models

We compared the ability of three models in predicting the presence of histologically confirmed localized UTUC (≤pT1 and the absence of lymph node metastasis in the final RNU pathologic specimen): a tumor grade- and stage-centered (GS) model based on tumor grade determined with URS, and invasiveness with computed tomography urography (CTU) or magnetic resonance imaging (MRI); the European Association of

Urology (EAU) and National Comprehensive Cancer Network (NCCN) model was based on the risk factors recommended by each guideline (Table 1).

Variable evaluation

Tumor grading was evaluated using the 2004 World Health Organization/International Society of Urologic Pathologists consensus classification. Tumor staging was based on the 2002 American Joint Committee on Cancer-International Union Against Cancer system. All cases were re-evaluated based on agreed upon criteria between pathologists of the UTUC collaboration. For cases prior to 2002 and 2004, restaging and regrading was performed. Based on urinary cytology findings, tumors were classified into high-grade versus not high-grade; cases of atypical urinary cytology, that were not clearly classified as high-grade, were classified into the not high-grade group. Tumor size was pathologically measured and used to divide tumors into two categories, because the size-based definition of high-risk varied between the EAU (>2 cm) and NCCN (>1.5 cm) guidelines.

Statistical analysis

The analyses were performed among patients with low-grade (URS) and low-stage (CTU/MRI) UTUC. After adjustments for other risk factors, univariable and multivariable logistic regression analyses were performed to determine whether a

particular risk factor was associated with the presence of pathologically localized UTUC. The sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy of the predictive models in evaluating the final pathologic stage were calculated. Area under the receiver operating characteristics curve (ROC-AUC) analyses were performed to examine the accuracy of each predictive model. We applied decision curve analysis (DCA) to evaluate the net benefit of different models in decision making within the clinically relevant range of threshold probabilities. The classification and regression tree (CART) method, a decision tree model, was also employed to develop an algorithm. Each root node was included PPV and bifurcated by repeatedly using the Gini coefficient, eventually resulting in terminal nodes. Each root node was bifurcated by repeatedly using the Gini coefficient, eventually resulting in terminal nodes. Statistical analyses were performed using STATA version 14.0 (Stata Corp., College Station, TX, USA) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P <0.05 was defined as statistically significant.

Results

Complete data on EAU risk factors were available for 745 patients, of whom tumor grade was not determinable in 185 patients based on pathologic evaluation using URS. These patients were excluded, leaving a total of 560 patients for analysis. The clinical and

pathological characteristics of the patients in our cohort are described in Table 2. In total, 283 (51%) and 277 (49%) patients had ≤pT1 and ≥pT2 disease, respectively, according to pathologic examinations of the surgical specimens. Concordance rate between tumor grades determined by URS and RNU was 69.6%. In the overall cohort, we identified 198 (35%) patients who showed low-grade tumors on URS and no muscle invasion on radiologic assessment. Of them, 139 (70%) and 59 (30%) patients had ≤pT1 and ≥pT2 disease, respectively.

As shown in Table 3, multivariable analysis revealed that none of the prognostic factors derived from either the EAU or NCCN guidelines were associated with the presence of localized UTUC tumors in patients showing low-grade and low-stage UTUC. The predictive performance of each model is shown in Table 4. The GS model, EAU model, and NCCN model identified 198 (35%), 33 (6%), and 24 (4%) patients, respectively; the accuracies were 64.1%, 52.1%, and 52.7%, respectively; and the AUCs were 71.2%, 74.6%, and 75.2% (comparison among models was shown in Supplementary Fig. 1), respectively. DCA revealed that within 0-20% of the threshold values, the net benefit of the three models was similar. In contrast, while the NCCN model was slightly superior within 20-40% of the threshold values, the GS and EAU models showed similar performance (Fig. 1). The results of the CART analysis are shown in Fig. 2. The most

decisive variable was urinary cytology findings. After splitting, terminal node 8 yielded the highest estimated probability (86%), resulting in 35 eligible patients (6%). We confirmed that the CART model with these four variables were not significantly associated with the presence of localized disease on a multivariable analysis (Supplementary Table.1).

Discussion

We found that the risk factors defined by the EAU and NCCN guidelines were not associated with the presence of localized UTUC tumors among patients with low-grade, low-stage UTUC. In other words, they did not improve the predictive value beyond clinical stage and grade by a statistically significant margin. The GS model, based on URS biopsy and imaging findings, provided a predictive accuracy comparable to that of the EAU and NCCN models while yielding a reasonable number of patients who could be considered for KSS. In addition, we developed a sequential weighted selection tree using a CART model for decision making and patient counseling.

In order to encourage clinicians to perform KSS without jeopardizing oncologic safety, guidelines have adapted restrictive risk management scenarios. There are inherent difficulties to accurately predict the tumor stage in patients with UTUC with a significant risk of understaging/missing pathologically advanced tumors. Such risk-management

strategies carefully integrate identified risk factors for patient management (14-16). Of these risk factors, tumor stage determined using imaging examinations has been found to be the most crucial independent factor (7, 17). Studies have shown that tumor grading by URS biopsy is also crucial because tumor grades are highly correlated with tumor stage in patients with UTUC (10, 18). However, due to the nature of such a rare entity, other risk factors have been identified largely based on experts' opinions and small, retrospective, single-institutional studies, resulting in low levels of evidence (19). For instance, urinary cytology findings have a poor predictive ability for muscle-invasive UTUC (sensitivity and PPV of 62% and 44%, respectively) (15). The value of hydronephrosis in predicting survival outcome also remains debatable (7). We found that none of the risk factors recommended by the EAU and NCCN guidelines, except for tumor grade and stage, significantly added value to risk prediction on multivariable analyses among patients with clinically low-grade, non-muscle invasive UTUC. Furthermore, although risk classification following the EAU and NCCN guidelines resulted in high specificities (96.4% and 98.6%, respectively), the sensitivities were extremely low (8.2% and 7.1%, respectively), and therefore, despite the fact that 281 patients (50%) of the entire cohort had localized disease, fewer eligible patients (6% and 4% of the entire cohort, respectively) were identified. Owing to these lower sensitivities,

some patients may have to unnecessarily undergo RNU (i.e., overtreatment) with significant health related consequences (20). Furthermore, both the EAU and NCCN models displayed a high AUC despite their low accuracy, suggesting that these models achieved a high PPV for non-muscle invasive UTUC at the cost of a high false negative rate. Meanwhile, the GS model that only included URS-based tumor grade and imaging-based stage showed the highest accuracy (64.1%), and it had better sensitivity (49.5%) and provided a higher number of eligible patients (35% of all patients) than the EAU and NCCN predictive models.

To date, several preoperative and postoperative models that focus on muscle invasive, non-organ confined UTUC, or survival outcomes have been developed (7, 10). However, to the best of our knowledge, only the EAU and NCCN guideline models aim to specifically identify patients with low-risk disease supposed to harbour non-muscle invasive UTUC. In our study, DCA showed that in the clinically plausible range of thresholds, the net benefits of the three predictive models were only marginally different, strongly suggesting that the GS model relying on clinical stage and grade only is of use in clinical practice.

Further, we also used a CART method to develop a sequential weighted selection tree that could assist in clinical decision-making and patient counseling. We found that as the

number of factors included increased, the possibility of detecting localized UTUC increased with decreased number of eligible patients. Interestingly, in contrast to the previous studies (21), in our selection tree, tumors >2 cm in size showed a higher possibility of being localized UTUC than those ≤2 cm. This finding may suggest that in patients with tumors presumed to be low-risk based on clinical stage and grade, tumors may grow only in the lumen without invasion to muscular layers, implying that tumor size might not be correlated with the presence of advanced UTUC (22). It is of utmost importance to balance the potential benefits of preserving the kidney with the risk of undertreatment, and to balance diagnostic accuracy with the number of eligible patients. Therefore, the optimal personalized treatment strategy (KSS vs RNU) should be chosen in a shared decision making based on patient counseling, taking into consideration factors such as the patients' life expectancy, comorbidities, and preferences.

So far, all guidelines have proposed risk factors based on widely used clinico-pathological features. Biomarkers that capture the biological and clinical potential of each tumor would help improve treatment by a large degree (23). Recently, in molecular characterization studies, a fibroblast growth factor receptor (FGFR) mutation was found at a high frequency in low-grade UTUC tumors (92%), providing insights that could lead to a potential improvement in survival outcomes (24, 25). Similarly, mRNA expression

subtypes may help refine tumor classification to drive therapy (26, 27). Further investigation to clarify the molecular profile may improve our understanding of UTUC biology and help in the development of rational and precise risk-stratification strategies as well as effective targets.

Every attempt to enhance diagnostic accuracy results in a decrease in the number of eligible patients. While our GS model is not perfect, it is quite simple to utilize. Considering the individualized patients' priorities such as avoiding RNU leading to dialysis or disease progression combined with the probabilities of localized UTUC obtained by the CART model, we could determine a successful individualized treatment for each case. Furthermore, clinicians could find their own acceptable probabilities using the CART model.

We acknowledge some limitations of this study. First, its retrospective nature could have introduced selection bias. Patients who received KSS treatment were not included in this study, thereby potentially underestimating the volume of patients eligible for KSS. However, the large majority of non-impactive cases underwent RNU during the study period, decreasing the size of selection bias and making a Will Rogers phenomenon unlikely. Moreover, the number of patients for whom risk assessment was performed using the EAU and NCCN model was small. This is supported by the substantial number

of patients who were confirmed to have pathologically localized UTUC (50%). Second, our findings showed a higher rate of tumor upgrading (54%) than previous studies (31-51%), but this is an inherent limitation and finding that varies across studies (28, 29). Third, we could not consider the probability of recurrence for KSS. Nevertheless, the GS model showed satisfactory predictive accuracy probably because imaging-based tumor staging complements this inherent limitation. Considering this and the multi-institutional nature of this study, our concept could be worthy of generalization and further investigation.

In conclusion, in this multi-institutional international cohort study of risk factors in UTUC tumors, we found that the risk factors proposed by the EAU and NCCN guidelines do not provide sufficient additive value in predicting a favourable pathologic outcome among patients with clinically low-grade, non-muscle invasive UTUC. The balance between avoiding unnecessary kidney loss (i.e., overtreatment) and that of undertreatment is delicate in clinical practice, needing biomarkers and patient factors as well as wishes. We believe that our stage- and grade-centered model provides a framework to improve the personalization treatment of UTUC patients sufficiently, achieving a more realistic balance between KSS and RNU. It could serve as an easy reproducible guide for discussions underlying a shared decision making with the patient regarding the optimal

management strategy for his tumor.

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Figure Legend

Figure 1. Decision Curve analysis illustrating the net benefit to predict non localized UTUC (muscle invasive or lymph node involvement) among the tumor grade- and stage-centered (GS) and EAU guidelines' and NCCN guidelines' models.

Figure 2. CART based weighed selection tree for prediction of non-muscle invasive UTUC.

Supplementary Figure 1. Prediction performance comparison of ≤pT1 UTUC tumor among the tumor grade- and stage-centered (GS) and EAU guidelines' and NCCN guidelines' models.